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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/726,348	12/01/2000	Ying-Fei Wei	PF220P1	3638

22195 7590 02/06/2002

HUMAN GENOME SCIENCES INC
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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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	9

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire One month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) 23 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-25 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-409-290/40029

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Invention II in Paper No. 10, filed 3/6/02 is acknowledged. The traversal is on the ground(s) that (1)the groups of inventions are not independent, and (2) the examination of the entire application would not constitute a burden to search. This is not found persuasive because with respect to point (1) above, the inventions are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. With respect to point (2) above, contrary to applicants' assertion that any search of the prior art in regard to group II will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26-77 are under consideration.

Formal Matters:

Applicants have drawn the Examiner's attention to certain copending applications. As the claims of such are not available to the Examiner at this time, no determination of double-patenting issues can be made. Such issues will be considered when said claims are made available.

Items AO and AR-AV cited on the information disclosure statement submitted 3/14/02, paper number 11, have not been considered, as no statement of relevance has been provided. The mere provision of a nucleic acid or protein sequence without either an alignment to the disclosed material

or explanation of relevance cannot be evaluated for relevancy to the claimed subject matter.

Objections and Rejections under 35 U.S.C. §§101 and 112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26-77 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification disclose a nucleic acid having SEQ ID NO:1, which is stated to encode a protein of SEQ ID NO: 2. The protein of SEQ ID NO: 2 is designated TGFα HIII, and is stated to belong to the EGF/TGFα family of cytokines. The specification discloses that the identification of TGFα HIII was made on the basis of amino acid sequence homology to human TGFα (page 3 lines 27-28), however no indication of a degree of homology nor any alignment to such are provided, and a sequence search of the amino acid sequence databases did not reveal any significant homology to such (i.e. none of the 'hits' returned was an alignment with TGFα). At page 10 of the specification, the sequence of the putative protein is analyzed, specifically that the protein is 229 amino acids in length, has 'significant' homology to TGFα , amphiregulin and cripto, and retains the six conserved cysteine residues of the EGF protein family. It is stated that residues 1-25 are a putative signal sequence which aids in secretion of the protein from the cell, that amino acids 126-177 are the 'active site' of the protein, that residues 178-204 are a transmembrane domain that may also be cleaved from the polypeptide such at the "putative soluble portion of the polypeptide of the present invention comprises amino acid through amino acid 177 of SEQ ID NO: 2." The specification further states (page 11 line 2) that the protein exhibits the highest degree of homology to TGFα , although what that degree is is not disclosed.

Disclosed uses for the claimed protein are as research reagents and materials for discovery of treatments and diagnostics for human disease , (page 115), "for characterization of receptors"

(page 116§3), for "restoration or enhancement of neurological functions diminished as a result of trauma or other damaging pathologies" based on the "widespread distribution of TGFα in various regions of the brain "suggesting that TGFα might play a physiological role in brain tissues" (page 116-118), to treat ocular disorders based on the implication of members of the TGFα gene family in such pathologies (page 116-118), as well as for antineoplastic use, liver regeneration or treatment of liver disfunction, wound healing, modulation of: angiogenesis, bone resorption, immune response, synaptic and neuronal effector functions, arachidonic acid cascade, terminal differentiation of target cells. alopecia (all on p.119), as well as page upon page of possible medical conditions which could be treated, including two and one-half pages of cardiovascular disorders (pp. 140-142).

These disclosures of utility do not meet the requirements of 35 U.S.C. § 101. 35 U.S.C. § 101 requires that there be either a well established utility for the claimed subject matter, or a specific, substantial and credible asserted utility; see the 2001 Utility Guidelines, 66 Fed. Reg. 1092. In the instant specification, applicants have presented a laundry list of thousands of medical conditions that *might* somehow, someday be shown to be associated in some way with the protein applicants designate TGFα HIII. However, the 'disclosure' of such a plethora of conditions is *not* disclosure of a specific utility, but merely a listing of any and all imaginable conditions.

The disclosed utilities fall into two general classes: (a) use as research reagents for discovery of treatments diagnostics and receptors, and (b) uses based on the projection that TGF α HIII will have similar activity to TGFα or other EGF family members , wherein possible uses are predicated on the activity or expression distribution of TGFα or other EGF family members. The use as research reagents for discovery of treatments diagnostics and receptors is a use for further research only, and is not sufficient to meet the requirements of 35 U.S.C. § 101. There are no disclosed conditions which can be treated or diagnosed based upon the information provided in the specification, such that use for such is not a readily available use, and is neither specific, substantial nor credible in the absence of such conditions. The use to find receptors for the protein is clearly a use for further research to find out more about the protein and its properties, and does not constitute a readily available use within the meaning of 35 U.S.C. § 101.

The uses based on the expression patterns or activity of TGFα or other EGF family members are not credible . They are based on the assumption that TGFα HIII would have equivalent activity and expression patterns to TGFα or other EGF family members, which is not a credible assertion. van Zoelen et al., in a chapter in "Growth Factors and Receptors", teach that EGF and TGFα are only 40% identical, but they bind the same receptor, and that such binding seems to require only a certain conformation; however, they also teach that mutations at residue 47 of EGF do not perturb three-dimensional structure, but result in EGF fully lacking biological activity, suggesting that "specific conformation of these growth factors is essential, but not sufficient for high affinity receptor binding" (page 87). van Zoelen et al. also teach that there are six known ligands for the EGF receptor, which have different properties, for example the transmembrane precursor form of HB-EGF has been shown to serve as the cellular target site for the diphtheria toxin (page 86). Further, they teach that there are three additional ligands for EGFR encoded by pox viruses, which share the overall structure of EGF and TGFα , including the spacing of the conserved cysteine residues, and that there is a family of proteins with a "so-called 'EGF like domain'", which "share the cysteine spacing with EGF receptor ligands, but lack amino acids essential for receptor binding, and as a consequence they do not interact with the EGFR." (Page 86). In view of the teachings in the art that (a) EGF family proteins are not highly conserved at the amino acid level, (b) that conservation of the six cysteine residues is not sufficient to indicate EGF receptor binding activity, and (c) that proteins that share the general structure of the EGF family of proteins are known which do not bind the EGF receptor, the assertion that TGFα HIII will bind the EGF receptor and thus have EGF/TGFα activity is not credible. Pimentel, in the *Handbook of Growth Factors, vol. II: Peptide Growth Factors* (1994) teaches that there are other types of TGF's in addition to TGFα and TGFβ. Pimentel discusses several different proteins which are classified as being TGF related, but each of which has different properties and functions (see pages 294-295). Therefore, the art does not support the assertion that merely because a protein has some (unspecified) degree of identity to EGF or TGFα and retains the six conserved cysteines that the protein can be accurately predicted to bind the EGF receptor or have a specific type of biological activity. Accordingly, the assertion that, based solely

on amino acid sequence analysis, TGFα HIII can be used for the same purposes as TGFα is not credible.

It is noted that the specification discloses 70 pages of prophetic examples to measure various aspects of activity, with no results at all. Finally, at page 270, it is disclosed that cell culture medium conditioned with TGFα HIII caused a level of proliferation of aortic smooth muscle cells "1.5 standard deviations above control" levels, and concludes that TGFα HIII "may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation", and thus would be useful for wound healing and angiogenesis. This assertion would not be considered credible by one skilled in the art because there insufficient information provided (i.e. how many replicates, what was the actual difference in cell proliferation observed, is such statistically significant), and because, as the specification itself makes clear, such is merely a preliminary result, in that it is not clear what cell type was affected, and therefore the result is a mere invitation to perform further experimentation to elucidate the properties and possible uses of TGFα HIII.

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a protein which has undetermined function or biological significance. Until some actual and *specific* activity can be attributed to the protein identified in the specification as TGFα HIII protein, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-77 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even *if* the specification were enabling of as protein of SEQ ID NO: 2 or a portion thereof which binds EGF receptor and acts as a mitogen, enablement would not be commensurate in scope with the claims, which include proteins which are 90% identical to SEQ ID NO: 2 or the protein encoded by the deposited clone and encode a protein which binds SEQ ID NO: 2 (claims 40 and 50), or comprises any 30 or 50 contiguous amino acid residues of SEQ ID NO: 2 (claims 64-65).

The claims encompass unspecified variant polynucleotides that hybridize under unspecified conditions and bind to a particular cell, though not necessarily via an EGF receptor, and which are not required to have any particular activity other than such binding. The specification merely discloses the nucleic acid of SEQ ID NO: 1, which is stated to encode SEQ ID NO: 2; no specific variants are disclosed, nor is there guidance as to how to make variants which retain biological activity, nor how to use variants which do not retain such activity. While the specification presents a very extensive prophetic disclosure of numerous conservative and non-conservative substitutions that can be made at each individual position of SEQ ID NO: 2, such is not considered to be specific guidance as to possible variants that may be made with a reasonable expectation of success, because such is merely a listing of thousands of possible changes that *could* be made, with no logic or reason to expect that the function of the resultant molecule would be conserved.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of

predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In this case, although proteins that bind and activate EGF receptors were known in the art, and the relative skill in the art of molecular biology is high, the predictability in the art of altering proteins and retaining function is relatively low, especially where, as in this case, the members of the protein family which bind EGF receptors have a low degree of conservation of amino acid sequences. Taken with the lack of working examples, the lack of *specific* direction or guidance as to alterations which could be made, the breadth of the claims, which in their current state read on a very large scope of proteins with only menial functional limitations, the specification fails to provide enablement commensurate in scope with the claims, even *if* enablement were found for proteins having SEQ ID NO: 2.

Claims 33, 35, 37-39, 50, 52, 55, and 57-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification and claims use the term "mature" protein or polypeptide, but the term is nowhere defined in the specification as originally filed. It is noted that in many cases, a "mature" protein is the full-length protein encoded by an isolated DNA clone with the exception that a signal sequence has been removed. However, in this case, where the disclosed protein is a member of the EGF family, the EGF family proteins are often much shorter than that, for example "mature" EGF is only 55 amino acids. Therefore, the specification fails to adequately describe what is meant by "mature" TGF α HIII.

Claims 50-59 and 74-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R.§1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 97342 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. See 37 C.F.R.§1.808(a)(2).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 33-39, 49, 50-59, 63, 69, 73, and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 39, 49, 59, 63, 69, 73, and 77 are indefinite because it is not clear what the phrase "expressing the polypeptide of claim X by a cell" indicates; such might read on any possible means of getting a cell to make such a polypeptide, or alternatively might be intended to indicate expression via recombinant DNA technology. It is not clear what limitations the process places on the claimed protein.

Claims 33, 35, 37-39, 50, 52, 55, and 57-59 are indefinite because the metes and bounds of

"mature" as applied to the disclosed protein are not clear, for reasons cited in the rejection of the same claims under 35 U.S.C. § 112, first paragraph for lack of adequate written description.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 60-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genbank Accession number HO2975.

Genbank Accession number HO2975, cited by applicants, is an est (expressed sequence tag) clone obtained from human placenta. The clone was disclosed as being in vector pT7T3D, which is an expression vector, and in host cells DH10B. The clone has 97.2% identity to the region of bases 364-816 of SEQ ID NO: 1, including complete identity in the region of bases 380-535, which encodes residues 126-177 of SEQ ID NO: 2.

The instant claims differ from the disclosure of the Genbank clone in that the Genbank disclosure does not make reference to expression of the protein encoded by the clone. However, it is noted that the clone disclosed in Genbank was contained in an expression vector, which indicates a vector which contains sequences necessary for the production of protein from the nucleic acid inserted into that vector. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to express protein encoded by the insert in clone HO2975 to obtain said protein for further study, or for the production of antibodies to said protein, such antibodies to be used to

isolate the protein itself, or for immunoassay. Because there is not complete identity, the expression of the entire clone would inherently produce a protein having heterologous sequences as compared to SEQ ID NO: 2. Further, because the region identified by the instant specification as being the active region is identical to that of HO2975, activity of the encoded protein would be inherent. To express such proteins is old and well known in the art, and indeed represents the use of the expression vector into which the cDNA inserts were cloned for its known and expected properties.

It is noted that applicants have submitted a declaration in the parent application, 08/778545, that was effective in overcoming this reference. Submission of a copy of that declaration in this case would be effective in overcoming this rejection.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Genbank Accession number H71660, cited by applicants, is an est (expressed sequence tag) clone obtained from human fetal liver spleen. The clone was disclosed as being in vector pT7T3D, which is an expression vector, and in host cells DH10B. The clone has 96.9% identity to the region of bases 382-868 of SEQ ID NO: 1, see attached alignment.

Farnham et al., reference AX cited by applicants, disclose a hamster protein the nucleotides encoding which have 24 bases' identity to SEQ ID NO: 1, but which would not encode either an active fragment or a fragment comprising at least 30 residues of SEQ ID NO: 2.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Spector via telephone number 703-746-5228. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

LMS
09/726348.1
4/16/02